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SIMPLE MODELING OF MATERNAL LEAD LEVELS DURING PREGNANCY: THE ROLE OF EXTRINSIC AND INTRINSIC FACTORS

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ABSTRACT

Dietary, socioeconomic, and medical factors, especially pregnancy and delivery events, can all explain considerable variance in lead levels during pregnancy and delivery. Although many prospective studies have controlled for socioeconomic variables in accounting for lead effects upon child development, dietary and medical factors during pregnancy appear to affect lead levels, and, as potentially important confounding variables, must be included in modeling lead effect in children.

It is clearly possible to detect many sources of environmental lead in prospective studies without direct environmental lead measurements. While such crude measures do not allow accurate determination of coefficients describing the quantitative contribution of each source to blood lead level, the public health value of the data in identifying important lead sources is great.

Lifetime maternal lead exposure may play a more important role in determining lead exposure of the fetus and young child than presently recognized. Public health implications of significant infant lead exposure during lactation require immediate study of the contribution of maternal bone stores of lead to lead in maternal milk.

INTRODUCTION

Blood lead level has been thought to reflect exposure vectors operating in the several weeks or months prior to the measurement.

These extrinsic factors undoubtedly play an important role in accounting for much of the variance in blood lead level. Less well studied is the effect of intrinsic factors, e.g., disease, pregnancy and aging, upon blood lead level.

Intrinsic factors can affect absorption and elimination of daily exposures, as well as mobilize lead from long-term compartments such as bone stores, and so explain additional variance in blood lead levels, unaccounted for by current sources of exposure.

Aside from small sample studies published in the past 25 years, there has been little attention paid to the variables accounting for blood lead levels during pregnancy. Studies during pregnancy are important because many prospective lead studies use maternal blood lead during pregnancy as a surrogate measure of fetal exposure without knowledge of the kinetics of maternal-fetal lead transfer, because pregnancy is a state with profound metabolic changes and because published studies have shown that maternal lead changes during pregnancy and maternal-cord lead relationships can explain more variance in infant outcome in the first 30 days of life than can absolute lead levels themselves.

We report data from the first large scale prospective study of blood lead levels during pregnancy in humans and additional data relating nursing patterns to blood lead levels of infants.

METHODS

Women seeking pre-natal medical attention at the National Institute of Perinatology in Mexico City around the 12th week of pregnancy were recruited into the study if they were not excluded by criteria based upon age, disease, psychosis, drug and alcohol use. A further cut was made at delivery, excluding premature, low birth weight, low Apgar score, and asphyxiated babies, as well as babies with major congenital anomalies and problems such as apnea and hyperbilirubinemia. The exclusion criteria insured healthy pregnancies and babies.

After complying with informed consent procedures women completed a medical history, including past pregnancies, socioeconomic questionnaires, nutrition and life style surveys. Venous blood samples were drawn for lead analysis every 8 weeks from week 12 of pregnancy, during regularly scheduled medical visits, and again from the mother and umbilical cord at delivery. Blood samples were taken from the children every 6 months for lead analysis. Most children's samples were venous, although at 6 months of age, some were capillary.

All blood samples were initially analyzed by anodic stripping voltammetry in duplicate. Samples with measured values below 5mcg/dl were reanalyzed in duplicate by atomic absorption spectrometry (AAS). All capillary samples, regardless of lead level, were analyzed by AAS. ESA Laboratories, Inc., Bedford, MA, performed all lead analyses.

Variables from the various questionnaires and the hospital medical records were a priori selected on the basis of their expected role in lead exposure or in pregnancy outcome and subsequent child development for univariate and bivariate statistical associations with blood lead. All variables associated with lead with Type I error probabilities of $p<0.10$ were retained for multivariate analysis.

Models of maternal blood lead at each stage of pregnancy as well as cord and child blood lead were constructed by using the significant variables above in forward, step-wise multiple regressions with backward elimination of variables whose probabilities fell below 0.10 upon entry of subsequent variables.

Additional models were constructed as above, but with the addition of the previous time adjacent blood lead level as an independent variable for several reasons. Prior blood lead levels will to some degree predict subsequent lead levels, depending upon elapsed time between measurements. And, to the extent that independent variables accounting for variance in the lead level modeled also account for variance in the immediately prior blood lead measurement, their effect against the modeled lead level will be reduced. This serves to sharpen the time scale in pregnancy during which we may detect variables that control any particular lead level.

RESULTS AND DISCUSSION

Maternal and Cord Lead Extrinsic Variables

All lead models during pregnancy include one variable in common, use of traditional, low temperature pottery. Traditional ceramic ware in Mexico is usually covered with leaded glaze, which readily leaches into food or drink. It is a documented source of frank lead intoxication in Mexico and other lands, and is a strong source of lead in the pregnant women studied here. Our group has measured 24 hour lead release from Mexican pottery exceeding 3000 ppm, using the FDA leaching test.

Other factors related to diet also make their appearance at various stages of pregnancy. These include milk drinking, which is associated with lower lead levels, soft drink use, associated with higher levels, and using canned food products, also associated with higher levels of lead.

Milk, due to its high calcium content, may protect against undue absorption of ingested lead in addition to providing a dietary source of calcium to the developing fetus. This latter proposed effect may prevent the mobilization of stored bone lead from the mother as might occur if the fetus were drawing bone calcium from the mother with a calcium deficient diet.

Canned foods in Mexico have been, until recently, predominantly made with lead soldered seals. In the last year the Mexican canning industry has voluntarily started conversion to welded seam cans. The exceptions have been canned milk products by Carnation and Nestlé, and some local brands of canned fruit juices. Imported canned foods, including Campbell's soup products from the United States, often contain soldered seals.

Alcohol use has been associated with higher maternal lead levels in other studies, and we find the same association here. The mechanism of the effect remains obscure, although reduced nutrition with increased drinking may provide a partial explanation.

Being born in Mexico City also is associated with higher maternal lead levels. This may reflect a lifetime of exposure to environmental lead in the city. Published air lead measurements in the 1970's and 1980's frequently exceeded 3 mcg/cubic meter for monthly averages in many parts of the city. Published data shows a relationship between air lead in Mexico City and lead levels in pregnant women. The extent of lead in dust and soil in Mexico City is at present unstudied, but is presumed high due to decades of use of highly leaded gasoline as well as notable stationary sources in the Valley of Mexico.

Intrinsic Variables

Increasing maternal age is associated with higher umbilical cord lead levels. This may reflect higher accumulated lead exposures in older women.

Prior pregnancies and abortions are both related to lower maternal lead levels. One possible explanation may be that prior pregnancies have mobilized bone stores of lead, with resulting lower amounts of bone lead available to be mobilized in the present pregnancy. Available published data indicates that aborted fetuses often have high lead levels.

Various problems during past or present pregnancies, such as history of premature births, high blood pressure (not treated with drugs), edema, cesarian delivery and still births are significant factors in maternal and cord lead levels. Mechanisms for these effects remain unknown, but their role as possible confounding factors of lead effect upon child development in prospective lead studies will soon be tested with these data.

Post-natal Lead

We selected two ages, 12 and 24 months, to model. Although sample size is still small, the models are interesting.

Socioeconomic, dietary and pregnancy and delivery variables all explain considerable variance in children's 12 month lead levels. Higher socioeconomic status is associated with lower lead, a finding replicated in other studies.

Grain consumption and use of prepared baby foods are also associated with lower 12 month lead levels, while soft drink consumption and drinking canned juices are associated with higher lead level. Fiber in the diet may affect lead absorption. Prepared baby foods may be provide early variety in the diet, with subsequent improved nutrition. Certainly soft drinks are without nutritional value and their association with increased 12 month lead level may reflect increased absorption by nutritionally deficient children. The source of lead in canned juices has been discussed above.

The finding of positive associations between complications during pregnancy and forceps delivery with lower 12 month lead appears at first sight paradoxical. However, if these two variables are associated with slower postnatal development, children suffering these pre and perinatal insults will have less contact with environmental sources such as dust lead and paint than the more developmentally advanced and mobile children not experiencing them.

Children at 24 months also show the effects of diet upon their lead levels. Milk and meat consumption appear to provide some protection from lead sources, while canned food consumption is positively related to lead level.

The most interesting feature in the 24 month lead model is the positive association between length of nursing and lead level. As shown in the chart the effect seems especially strong for nursing beyond 12-24 months. Although data being collected on maternal milk lead in Mexico is not yet available, maternal milk may be a significant source of early childhood lead exposure in that country. Both current and lifetime maternal lead exposure may interact with maternal dietary status to influence the amount of lead in maternal milk through mechanisms similar to those proposed above during the pregnancy.

SUMMARY

Serial maternal blood samples in the Mexico City Prospective Lead Study have been used to construct multivariate models of blood lead during consecutive 8 week periods of the pregnancy from 12 weeks to the moment of birth.

These models confirm that personal habits, such as use of traditional lead-glazed ceramic ware, eating canned foods, and frequency of milk consumption, and factors intrinsic to the mother and pregnancy, such as complications during pregnancy, type of delivery, age birthplace, residence time in Mexico City, number of previous pregnancies and live births, can all explain variance of maternal and cord blood lead.

Two methods of model construction were used, both using forward, step-wise multiple regressions. In the first, separate models were constructed for the blood lead levels at each stage of pregnancy without considering prior blood lead levels. In the alternate approach, the immediately prior blood lead level was entered into the regression first, thereby adjusting the blood level of interest by the correlation between the two. Models were then constructed on the adjusted lead values.

Changes and commonalities among the models reveal the variable role of environmental and intrinsic factors in accounting for maternal lead level throughout the pregnancy and for the relationship between maternal and cord lead at delivery.

Additional models of lead levels of 24 month old children reveal the possible role of breast milk in lead exposure. These results have implications for populations currently exposed to lead, as well as for those whsoe lead exposure has been reeduced in the past.

Model Fitting Results for **LOG Pb 12 Weeks**

Independent variable	Coefficient	Std. Error	t-value	Sig.level
CONSTANT	3.735481	0.361025	10.3469	0.0000
Home remedies, last 3 months	0.209505	0.089171	2.3495	0.0196
Birth place (Mexico City)	0.227897	0.101053	2.2552	0.0250
High blood pressure, this preg.	0.293972	0.125317	2.3458	0.0198
Economic dependents	-0.195465	0.082436	-2.3711	0.0185
Low Temp. ceramic ware	0.141805	0.081287	1.7445	0.0823

R-SQ. (ADJ.) = 0.0690 SE= 0.628826 MAE= 0.467966 DurbWat= 1.804
253 observations.

Model fitting results for: LOG Pb 20 Weeks

Independent variable	Coefficient	Std. Error	t-value	Sig. level
CONSTANT	2.265265	0.210736	10.7493	0.0000
Alcohol, frequency	0.135461	0.079148	1.7115	0.0881
Low temp. ceramic ware	0.396723	0.08318	4.7695	0.0000

R-SQ. (ADJ.) = 0.0764 SE= 0.692533 MAE= 0.505904 DurbWat= 1.688
291 observations.

Independent variable	Coefficient	Std. Error	t-value	Sig. level
CONSTANT	1.728912	0.280151	6.1714	0.0000
LOG Pb 12 Weeks	**0.379304**	**0.076992**	**4.9266**	**0.0000**
Coffee	0.192561	0.104685	1.8394	0.0674
Low temp. ceramic ware	0.241331	0.096072	2.5120	0.0129
Stillbirth	0.339961	0.208435	1.6310	0.1046

R-SQ. (ADJ.) = 0.1663 SE= 0.640751 MAE= 0.456629 DurbWat= 1.888
191 observations

Model fitting results for: **LOG Pb 28 Weeks**

Independent variable	Coefficient	Std. Error	t-value	Sig.level
CONSTANT	3.686687	0.339783	10.8501	0.0000
Previous pregnancies, number of	-0.108354	0.035819	-3.0251	0.0027
Canned milk	0.10538	0.034602	3.0455	0.0026
Soft drink	0.074318	0.033203	2.2383	0.0260
Birth place (Mexico City)	0.4458	0.111739	3.9897	0.0001
Coffee	0.32734	0.104583	3.1300	0.0019
Problems previous pregnancies	0.222836	0.099764	2.2336	0.0264
Low temp. ceramic ware	0.35514	0.088223	4.0255	0.0001

R-SQ. (ADJ.) = 0.1897 SE= 0.702289 MAE= 0.534865 DurbWat= 1.772
269 observations.

Independent variable	Coefficient	Std. Error	t-value	Sig. level
CONSTANT	2.334656	0.340369	6.8592	0.0000
LOG Pb 20 Weeks	**0.417241**	**0.066031**	**6.3189**	**0.0000**
Soft drink	0.087556	0.035772	2.4477	0.0152
Low temp. ceramic ware	0.222638	0.09776	2.2774	0.0238
Birth place (Mexico City)	0.366348	0.113361	3.2317	0.0014
Previous pregnancies, # of	-0.076212	0.033225	-2.2938	0.0228
Coffee	0.321821	0.108758	2.9591	0.0034

R-SQ. (ADJ.) = 0.2763 SE= 0.667956 MAE= 0.485837 DurbWat= 1.943
215 observations.

Model fitting results for: **LOG Pb 36 Weeks**

Independent variable	Coefficient	Std. Error	t-value	Sig.level
CONSTANT	3.30571	0.332392	9.9452	0.0000
Previous abortions, number of	-0.160476	0.050489	-3.1785	0.0017
Milk, frequency	-0.100335	0.04564	-2.1984	0.0290
Soft drink	0.068708	0.034013	2.0201	0.0446
Alcohol drunk each occasion	0.198524	0.076084	2.6093	0.0097
Birth place (Mexico City)	0.225191	0.111148	2.0261	0.0440
Problems in previous pregnancies	0.212695	0.092428	2.3012	0.0223
Low temp. ceramic ware	0.450639	0.089982	5.0081	0.0000

R-SQ. (ADJ.) = 0.1762 SE= 0.659405 MAE= 0.497077 DurbWat= 1.841
227 observations.

Independent variable	Coefficient	Std. Error	t-value	Sig. level
CONSTANT	1.779332	0.225923	7.8758	0.0000
LOG Pb 28 Weeks	**0.46206**	**0.059625**	**7.7494**	**0.0000**
Previous abortions, # of	-0.106973	0.047894	-2.2335	0.0268
Low temp. ceramic ware	0.266576	0.094599	2.8180	0.0054
Ocupation of family head	-0.048368	0.028061	-1.7237	0.0865

R-SQ. (ADJ.) = 0.3386 SE= 0.602182 MAE= 0.426265 DurbWat= 1.723
182 observations.

Model fitting results for: **LOG Pb Mother at delivery**

Independent variable	Coefficient	Std. Error	t-value	Sig.level
CONSTANT	3.275081	0.233486	14.0269	0.0000
Economic dependents	-0.210549	0.082529	-2.5512	0.0114
Birth place (Mexico City)	0.321546	0.117092	2.7461	0.0065
Subway, time traveling in	0.1964	0.101578	1.9335	0.0543
Low temp. ceramic ware	0.337199	0.093687	3.5992	0.0004

R-SQ. (ADJ.) = 0.1071 SE= 0.715907 MAE= 0.526405 DurbWat= 1.845
246 observations.

Independent variable	Coefficient	Std. Error	t-value	Sig. level
CONSTANT	0.175078	0.310798	0.5633	0.5740
LOG Pb 36 Weeks	**0.498249**	**0.060177**	**8.2798**	**0.0000**
Nuts	0.112386	0.046385	2.4229	0.0165
Cesarean	-0.228887	0.10186	-2.2471	0.0260
Edema, this pregnancy	-0.179452	0.097318	-1.8440	0.0671

R-SQ. (ADJ.) = 0.3090 SE= 0.604822 MAE= 0.442418 DurbWat= 1.737
161 observations.

Model fitting results for: **LOG Pb Umbilical cord**

Independent variable	Coefficient	Std. Error	t-value	Sig.level
CONSTANT	1.42871	0.499958	2.8577	0.0047
Age of the mother	0.021265	0.007962	2.6708	0.0081
Milk, frequency	-0.156383	0.049479	-3.1606	0.0018
Previous premature	-0.264135	0.107425	-2.4588	0.0147
Alcohol drunk last month	-0.350757	0.135448	-2.5896	0.0103
Canned meat	0.319414	0.157514	2.0278	0.0438
Low temp. ceramic ware	0.414535	0.095664	4.3332	0.0000

R-SQ. (ADJ.) = 0.1776 SE= 0.690896 MAE= 0.519635 DurbWat= 1.944
221 observations.

Independent variable	Coefficient	Std. Error	t-value	Sig.level
CONSTANT	1.087441	0.33737	3.2233	0.0015
LOG Pb Mother at delivery	**0.662443**	**0.051288**	**12.9162**	**0.0000**
Term pregnancies, # of	0.108446	0.038092	2.8469	0.0049
Previous premature, # of	-0.267361	0.082837	-3.2276	0.0015
Hi blood pressure, this pregnancy	0.210379	0.113223	1.8581	0.0647
Milk	-0.099812	0.036812	-2.7114	0.0073
Low temp. ceramic ware	0.145525	0.079741	1.8250	0.0696

R-SQ. (ADJ.) = 0.5464 SE= 0.496641 MAE= 0.373714 DurbWat= 2.043
192 observations.

Model Fitting Results for **LOG Pb 12 Months**

Independent variable	Coefficient	Std. Error	t-value	Sig. level
CONSTANT	2.075126	0.273711	7.5815	0.0000
Socioeconomic level	-0.0547	0.031916	-1.7139	0.0887
Cereal	-0.071681	0.027848	-2.5740	0.0111
Soft drinks consummed by the kid	0.061027	0.030872	1.9768	0.0500
Canned juices	0.068314	0.039274	1.7394	0.0841
Processed baby food	-0.075444	0.029803	-2.5314	0.0124
Forceps	-0.200622	0.105013	-1.9104	0.0581
Complications this pregnancy	-0.219025	0.082013	-2.6706	0.0084

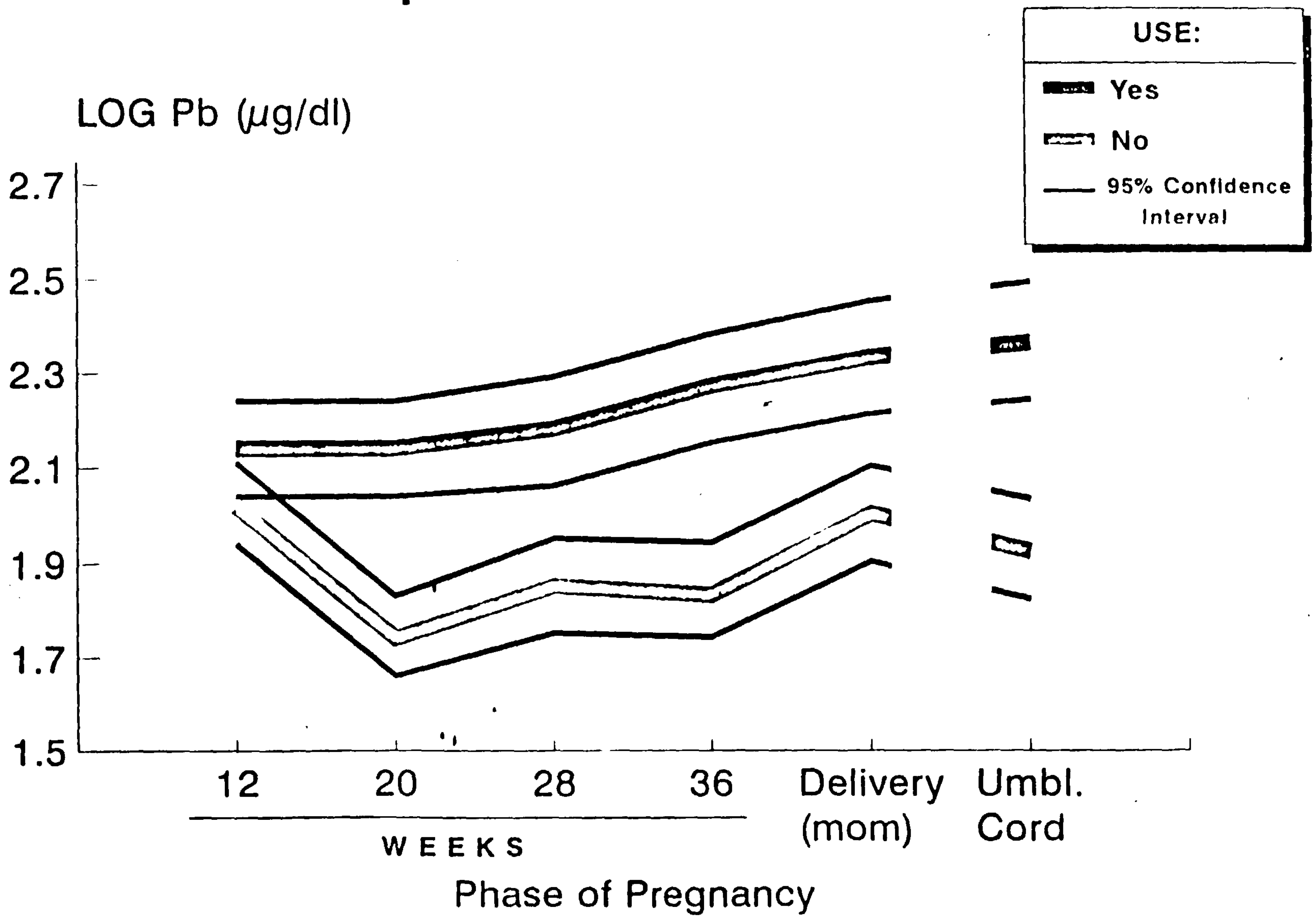
R-SQ. (ADJ.) = 0.1967 SE= 0.482358 MAE= 0.356316 DurbWat= 1.636
153 observations.

Model fitting results for: **LOG Pb 24 Months**

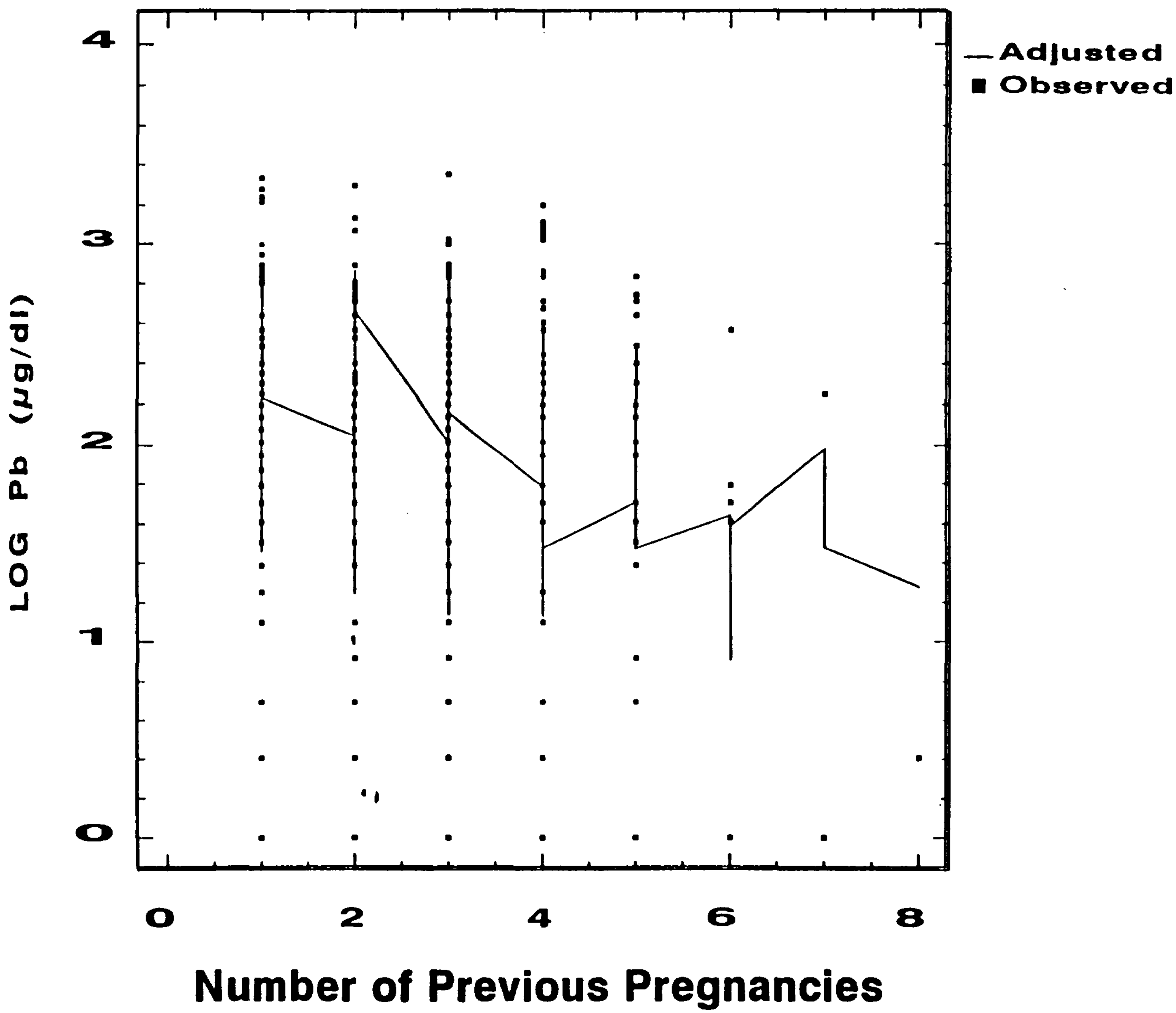
Independent variable	Coefficient	Std. Error	t-value	Sig. level
CONSTANT	3.331844	0.271183	12.2863	0.0000
Breastfeeding, time	0.017917	0.007299	2.4547	0.0157
Milk	-0.114652	0.039965	-2.8688	0.0049
Education of mother	-0.066924	0.029938	-2.2354	0.0274
Meat	-0.098283	0.0518	-1.8973	0.0604
Canned milk	0.05516	0.02085	2.6456	0.0094
Canned juices	0.081286	0.040641	2.0001	0.0480

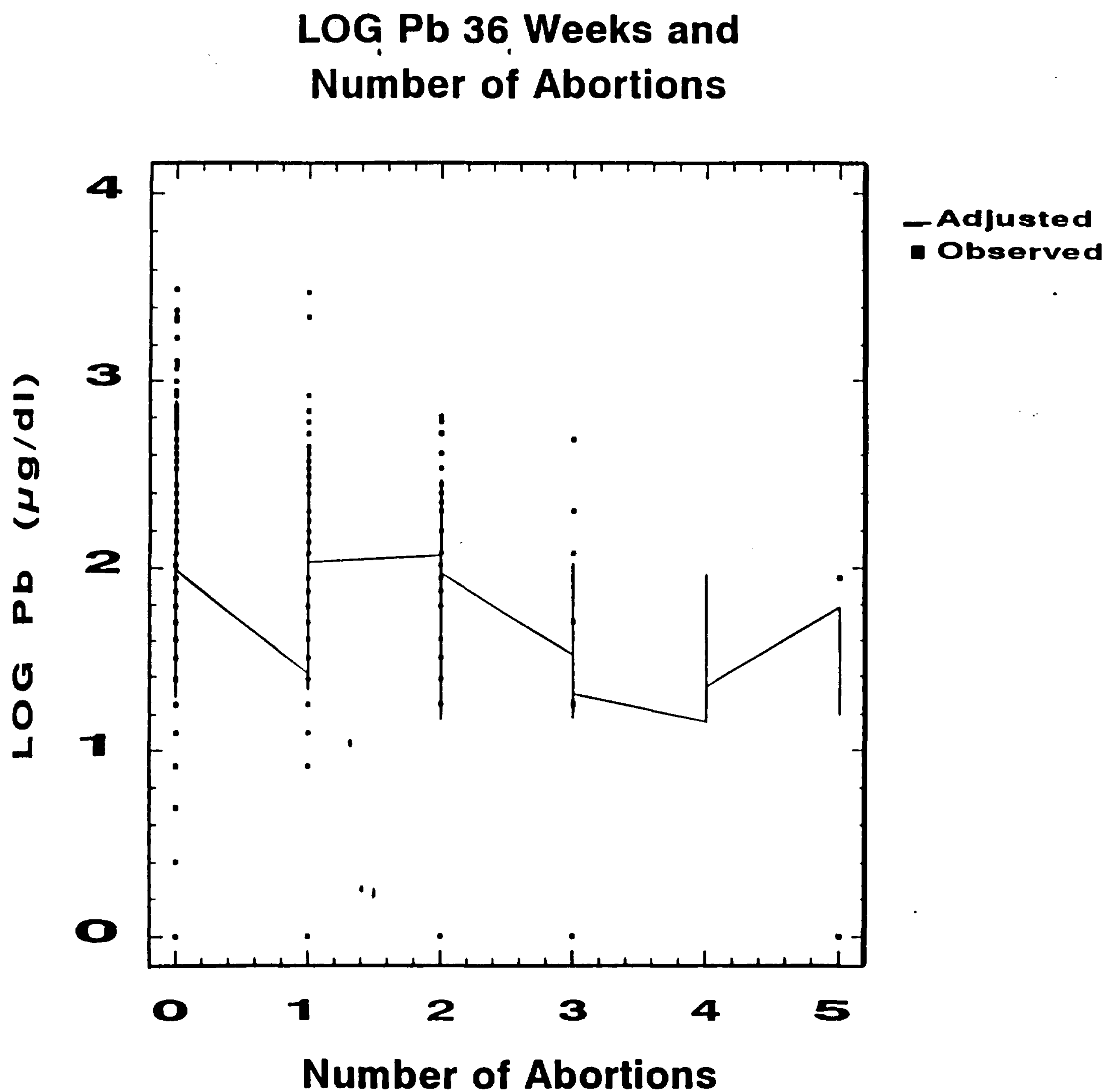
R-SQ. (ADJ.) = 0.2440 SE= 0.402370 MAE= 0.305753 DurbWat= 2.122
116 observations.

LOG Lead Levels at During Pregnancy and Low Temperature Ceramic Ware Use

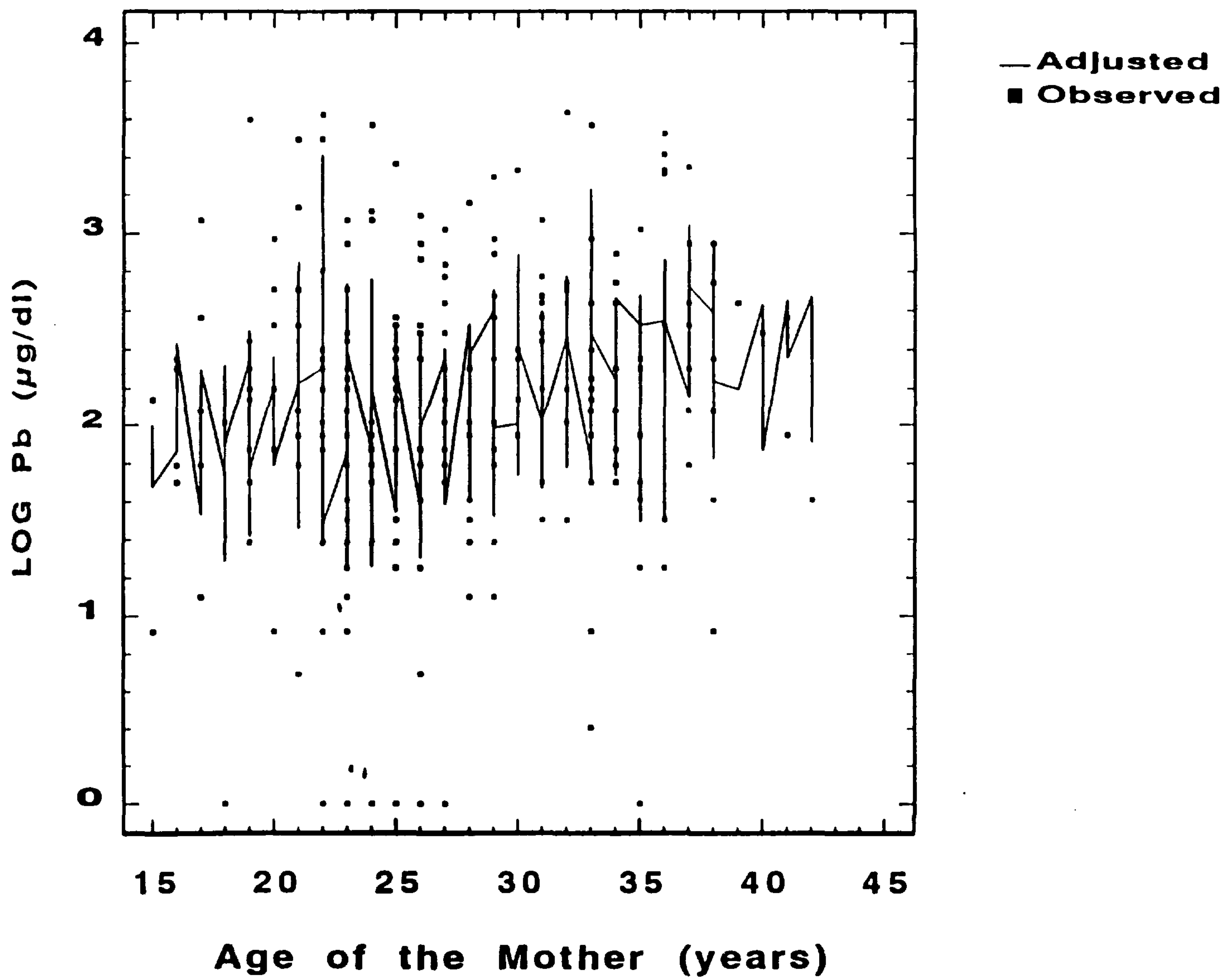


LOG Pb 28 Weeks and Previous Pregnancies




LOG Pb 36 Weeks and
Number of Abortions
LOG Pb (µg/dl)
Number of Abortions
Adjusted
Observed
0
1
2
3
4
5

LOG Pb Umbilical Cord and Age of the Mother



LOG Pb 24 Month and Breast-feeding